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L7: Entry 12 of 15 File: USPT Dec 25, 2001

Dec. 22 1997 filed 08/08/1997 to 5,626,843 2-26-93

DOCUMENT-IDENTIFIER: US 6333032 B1
TITLE: Treatment of autoimmune diseases

Brief Summary Text (9):
In addition, increased circulating levels of TNF.alpha. have been found to be associated with disease progression in patients with multiple sclerosis (Shariff et al., N. Engl. J. Med. 325 (7):467-472 (1992)); while increased serum levels of soluble TNF receptor and interferon .gamma.("INF.gamma.") have been independently correlated with disease activity in individuals, e.g., those with systemic lupus erythematosus (Aderka et al., Arthritis Rheum. 36(8):1111-1120 (1993); Machold et al., J. Rheumat. 17 (6):831-832 (1990)). The spontaneous release of interferon and TNF in HIV-positive subjects (Vilcek et al., In AIDS: The Epidemic of Karposi's Syndrome and Opportunistic Infections, A. E. Friedman-Kien & L. J. Laubenstein, eds. Masson Publishing, New York, N.Y., 1986; Hess et al., Infection 19, Suppl. 2:S93-97 (1991); Biglino et al., Infection 19 (1):11/7-11/17 (1991)), and the decline seen in the serum levels of TNF-.alpha. in RA patients following long term administration of the disease modifying drug sulfasalazine (Danis et al., Ann. Rheum. Diseas. 51(8):946 (1992)), further suggest that the concentrations of cytokines and/or their receptors is reflected in the clinical course of autoimmune disease.

Brief Summary Text (12):
Recognition of the important role of cytokines in autoimmune disease has fostered the development of a new generation of therapeutic agents to modulate cytokine activity. Preliminary results of trials in which anti-interferon polyclonal antibodies were administered to a small group of rheumatoid patients suggest improvement in both the clinical and the laboratory manifestations of the disease (Skurkovich et al., Annals of Allergy 39:344-350 (1977)). Moreover, proteins, such as polyclonal antibodies and soluble receptors targeted against interferons and TNF-.alpha. are currently being evaluated in clinical trials for the treatment of RA and other autoimmune diseases. The administration of monoclonal antibodies to TNF-.alpha. has provided encouraging early results in the treatment of patients with severe RA (Elliott et. al., J. Cell. Biochem., Suppl. 17B:145 (1993); Elliott et al., Lancet 344:1105-1110 (1994)). Also positive preliminary results were achieved in AIDS patients given antibodies or other agents to reduce the level of circulating IFN.alpha. in the body (Skurkovich et al., 1994; Gringeri et al., 1996). However, because autoimmune diseases are complex, often characterized by multiple cytokine abnormalities, effective treatment appears to require the simultaneous administration or utilization of several agents, each targeting a specific cytokine pathway or its by-product. To meet this need, the methods of treatment of the present invention include not only the use of specific antibodies, but also provide pleiotrophic autoimmune inhibitors, including antibodies to cytokines and HLA class II antigens, and antigens for the removal of autoantibodies to target cells or DNA. The use of these antibodies and antigens as disclosed in the present invention results in the removal, neutralization or inhibition of the pathogenic cytokine(s), HLA class II antigens, and/or autoantibody(ies) to target cells or DNA from the autoimmune patient, thereby significantly improving the quality of life of the individual.

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Brief Summary Text (50):
Autoimmune conditions for which the method of the present invention is applicable include, for example, AIDS, atopic allergy, bronchial asthma, eczema, leprosy, schizophrenia, inherited depression, transplantation of tissues and organs, chronic fatigue syndrome, Alzheimer's disease, Parkinson's disease, myocardial infarction, stroke, autism, epilepsy, Arthus's phenomenon, anaphylaxis, and alcohol and drug addiction. In the above-identified autoimmune conditions, the tissue affected is the primary target, in other cases it is the secondary target. These conditions are partly

or mostly autoimmune syndromes. Therefore, in treating them, it is possible to use the same methods, or aspects of the same methods that are herein disclosed for treating AD, sometimes in combination with other methods.

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L7: Entry 15 of 15 File: USPT Mar 30, 1999

DOCUMENT-IDENTIFIER: US 5888511 A
TITLE: Treatment of autoimmune diseases, including AIDS

Brief Summary Text (10):
In addition, increased circulating levels of TNFa have been found to be associated with disease progression in patients with multiple sclerosis (Shariffet al., N. Engl. J. Med. 325(7):467-472 (1992)); while increased serum levels of soluble TNF receptor and interferon .gamma. ("INF.gamma.") have been independently correlated with disease activity in individuals, e.g., those with systemic lupus erythematosus (Aderka et al., Arthritis Rheum. 36(8):1111-1120 (1993); Machold et al., J. Rheumat. 17(6):831-832 (1990)). The spontaneous release of interferon and TNF in HIV-positive subject,, (Vilcek et al., In AIDS: The Epidemic of Karposi's Syndrome and Opportunistic Infections A. E. Friedman-Kien & L. J. Laubenstein, eds. Masson Publishing, New York, N.Y., 1986; Hess et al., Infection 19, Suppl. 2:S93-97 (1991); Biglino et al., Infection 19 (1):11/7-11/17 (1991)), and the decline seen in the serum levels of TNF-.alpha. in RA patients following long term administration of the disease modifying drug sulfasalazine (Danis et al., Ann. Rheum. Diseas. 51(8):946 (1992)), further suggest that the concentrations of cytokines and/or their receptors is reflected in the clinical course of autoimmune disease.

Brief Summary Text (13):
Recognition of the important role of cytokines in autoimmune disease has fostered the development of a new generation of therapeutic agents to modulate cytokine activity. Preliminary results of trials in which anti-interferon polyclonal antibodies were administered to a small group of rheumatoid patients suggest improvement in both the clinical and the laboratory manifestations of the disease (Skurkovich et al., Annals of Allergy 39:344-350 (1977)). Moreover, proteins, such as polyclonal antibodies and soluble receptors targeted against interferons and TNF-.alpha. are currently being evaluated in clinical trials for the treatment of RA and other autoimmune diseases. The administration of monoclonal antibodies to TNF-.alpha. has provided encouraging early results in the treatment of patients with severe RA (Elliott et. al., J. Cell. Biochem., Suppl. 17B: 145 (1993); Elliott et al., Lancet 344: 1105-1110 (1994)). Also positive preliminary results were achieved in AIDS patients given antibodies or other agents to reduce the level of circulating IFN.alpha. in the body (Skurkovich et al., 1994; Gringeri et al., 1996). However, because autoimmune diseases are complex, often characterized by multiple cytokine abnormalities, effective treatment appears to require the simultaneous administration or utilization of several agents, each targeting a specific cytokine pathway or its by-product. To meet this need, the methods of treatment of the present invention include not only the use of specific antibodies,. but also provide pleiotrophic autoimmune inhibitors, including antibodies to cytokines and HLA class II antigens, and antigens for the removal of autoantibodies to target cells or DNA. The use of these antibodies and antigens as disclosed in the present invention results in the removal, neutralization or inhibition of the pathogenic cytokine(s), HLA class II antigens, and/or autoantibody(ies) to target cells or DNA from the autoimmune patient, thereby significantly improving the quality of life of the individual.

Brief Summary Text (51):
Autoimmune conditions for which the method of the present invention is applicable include, for example, AIDS, atopic allergy, bronchial asthma, eczema, Behget's syndrome, leprosy, schizophrenia, inherited depression, transplantation of tissues and organs, chronic fatigue syndrome, Alzheimer's disease, Parkinson's disease, myocardial infarction, stroke, autism, epilepsy, Arthus's phenomenon, anaphylaxis, and alcohol and drug addiction. In the above-identified autoimmune conditions, the tissue affected is the primary target, in other cases it is the secondary target. These conditions are

partly or mostly autoimmune syndromes. Therefore, in treating them, it is possible to use the same methods, or aspects of the same methods that are herein disclosed for treating autoimmune disease, sometimes in combination with other methods.